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Towards an analytic solution for pulsed CEST

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Abstract

Chemical exchange saturation transfer (CEST) is an imaging method based on magnetization exchange between solutes and water. This exchange generates changes in the measured signal after off-resonance radiofrequency irradiation. Although the analytic solution for CEST with continuous wave (CW) irradiation has been determined, most studies are performed using pulsed irradiation. In this work, we derive an analytic solution for the CEST signal after pulsed irradiation that includes both short-time rotation effects and long-time saturation effects in a two-pool system corresponding to water and a low-concentration exchanging solute pool. Several approximations are made to balance the accuracy and simplicity of the resulting analytic form, which is tested against numerical solutions of the coupled Bloch equations and is found to be largely accurate for amides at high fields, but less accurate at the higher exchange rates, lower offsets and typically higher irradiation powers of amines.

Graphical abstract

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We derive an analytic solution for the CEST signal after pulsed irradiation that includes both short-time solute rotation effects and long-time saturation effects. Several approximations are made to balance the accuracy and simplicity of the resulting analytic form, which is tested against numerical solutions of the coupled Bloch equations and is found to be largely accurate for amides at high fields, but less accurate at the higher exchange rates, lower offsets, and typically higher irradiation powers of amines.

Keywords

analytic; CERT; CEST; exchange

1 | INTRODUCTION

Chemical exchange saturation transfer (CEST) is an imaging method based on magnetization exchange between solutes and water. The image contrast is sensitive to the solute concentration and exchange rate, and variants of the method have been used to image proteins,¹ pH,² creatine,³ glucose⁴ and other metabolites. A core issue in many of these studies, however, is the degree of specificity. That is, the question is to what degree the image reflects solute concentration and exchange *versus* water or macromolecular characteristics, and, correspondingly, what pulse sequence and metric are optimum to achieve such specificity. Although numerical solutions (via numerical integration of the differential equations) can help to address these questions by determining the signal for a given set of sequence and tissue parameters, an analytic solution of the measured signal provides a much greater degree of understanding, especially if the analytic solution is relatively simple. In addition, analytic solutions can be used to calculate the signal much more rapidly than can numerical integration, which is important when inverting the signal equation to fit the underlying tissue parameters.

The analytic solution for CEST with continuous wave (CW) saturation has been determined.^{5,6} However, human scanners typically cannot irradiate continuously and, instead, use pulsed

saturation. Further, pulsed irradiation potentially allows for unique contrast generation beyond that which is possible with CW irradiation by isolating exchange effects from rotated *versus* saturated magnetization.^{7–9} Thus far, there have been several published analytic solutions for pulsed saturation, but all have significant limitations. Often, solutions derived for CW saturation are used to analyze pulsed saturation.^{10,11} Recently, solutions that explicitly account for pulsed saturation have been derived, but with highly limited regimes, e.g. using repeated hard pulses¹² or limited to very fast exchange.¹³ All of these methods ignore solute rotation and cannot account for simple observed effects, such as the optimum sensitivity when using a train of 180° pulses.¹⁴ The chemical exchange rotation transfer (CERT) approach⁷ implies a general form of the solution, with rotation effects being a function of the integral of the irradiation field amplitude, and direct saturation and macromolecular magnetization transfer (MT) effects being a function of the integral of the square of the amplitude. However, without an explicit analytic form, the relationship between the tissue parameters (and, in particular, the solute exchange rate, offset and relaxation rates) and the corresponding signal is unclear, making effective pulse sequence design difficult.

In this work, we derive an analytic solution for the CEST signal after pulsed saturation that includes both short-time rotation effects and long-time saturation effects in a two-pool system corresponding to water and a low-concentration exchanging solute pool. Several approximations are made to balance the accuracy and simplicity of the resulting analytic form, which is then tested against numerical solutions of the coupled Bloch equations to determine the applicable regime. In addition, a peripheral, but notable, side result is the determination of analytic forms for the evolution rates during CW irradiation, including the decay rate transverse to the effective field ($R_{2\rho}$).

2 | THEORY AND RESULTS

2.1 | The experiment

A CEST experiment measures the water magnetization as a function of the irradiation frequency offset, as illustrated in Figure 1A. The subscripts ‘a’ and ‘b’ refer to water and a low-concentration solute, respectively, with corresponding normalized steady-state z -magnetization (Z^s), relaxation rates (R_1 and R_2), resonant frequency (ω), irradiation frequency offset (ω) and exchange rate (k). f_b is the ratio of the pool sizes. For pulsed irradiation, the pulse timings (t_p and t_d) and the corresponding values for the approximating sequence used in the derivation below ($t_{p,\text{hard}}$ and $t_{d,\text{hard}}$) are defined in Figure 1B.

2.2 | Final result

For those whose interest lies in application rather than derivation, we start with the final result: the normalized steady-state water z -magnetization under pulsed irradiation ($Z_a^{\text{ss, pul}}$) is:

$$Z_a^{ss,pul} = \frac{P^2 R_{1a}}{R_{1\rho,pul}}. \quad (1)$$

Equation 1 has the same form as the solution to the CW case,⁵ but with a projection factor:

$$P^2 = \frac{t_{p,hard} \cos^2 \theta_a + t_{d,hard}}{t_{p,hard} + t_{d,hard}}, \quad (2)$$

and with an effective rotating frame relaxation rate $R_{1\rho,pul}$ that has a simple form when assuming irradiation at large offsets from the water resonance:

$$R_{1\rho,pul}|_{\Delta\omega_a = \infty} = R_{1\rho} DC_{hard} + R_{1a}(1 - DC_{hard}) + \frac{1}{t_p + t_d} f_b (1 - e^{-k_b t_{d,hard}})$$

$$\times \frac{\omega_{1,hard}^2 + \Delta\omega_b^2}{\omega_{1,hard}^2 + \Delta\omega_b^2 + k_b^2}$$

$$\times \frac{1 - e^{-R_{2\rho,b} t_{p,hard}} \cos(\omega_{eff,b} t_{p,hard}) - e^{-R_{2\rho,b} t_{p,hard}} \left(\frac{k_b}{\sqrt{\omega_{1,hard}^2 + \Delta\omega_b^2}} \right) \sin(\omega_{eff,b} t_{p,hard})}{1 - e^{-k_b t_{d,hard}} - R_{2\rho,b} t_{p,hard} \cos(\omega_{eff,b} t_{p,hard}) + \frac{\Delta\omega_b^2}{\omega_{1,hard}^2} (1 - e^{-k_b t_{d,hard}} - R_{1\rho,fast} t_{p,hard})}.$$

$$(3)$$

This result simplifies further when the irradiation is applied at the solute resonance:

$$R_{1\rho, \text{pul}}^{\Delta\omega_b=0, \Delta\omega_a=\infty} = R_{1\rho} \text{DC}_{\text{hard}} + R_{1a}(1 - \text{DC}_{\text{hard}}) + \frac{1}{t_p + t_d} f_b(1 - e^{-k_b t_d, \text{hard}}) \\ \times \frac{\omega_{1, \text{hard}}^2}{\omega_{1, \text{hard}}^2 + k_b^2} \frac{\left(1 - e^{-R_{2\rho, b} t_p, \text{hard}} \cos(\omega_{\text{eff}, b} t_p, \text{hard}) - e^{-R_{2\rho, b} t_p, \text{hard}} \left(\frac{k_b}{\omega_{1, \text{hard}}}\right) \sin(\omega_{\text{eff}, b} t_p, \text{hard})\right)}{(1 - e^{-k_b t_d, \text{hard}} - R_{2\rho, b} t_p, \text{hard} \cos(\omega_{\text{eff}, b} t_p, \text{hard}))}$$

(4)

These results use the pulse sequence definitions:

$$\text{DC}_{\text{hard}} = \frac{t_{p, \text{hard}}}{t_{p, \text{hard}} + t_{d, \text{hard}}} = \frac{t_p}{t_p + t_d} \frac{p_1^2}{p_2} = \text{DC} \frac{p_1^2}{p_2} \quad t_{p, \text{hard}} = t_p \frac{p_1^2}{p_2} \quad t_{d, \text{hard}} = t_d + t_p \left(1 - \frac{p_1^2}{p_2}\right) \quad (5)$$

$$\text{pulse repetition time} = t_p + t_d = t_{p, \text{hard}} + t_{d, \text{hard}} \quad \omega_{1, \text{hard}} = \frac{p_2}{p_1^2} \omega_{1, \text{avg}} = \frac{p_2}{p_1^2} \frac{1}{t_p} \int_0^{t_p} \gamma B_1(t) dt,$$

(6)

where $\omega_{1, \text{avg}}$ is the average of γB_1 over the shaped irradiation pulse, p_1 is the ratio of the average amplitude to the maximum amplitude of the irradiation pulse and p_2 is the ratio of the average of the square of the amplitude to the square of the maximum amplitude of the

irradiation pulse. Finally, $\cos^2 \theta_a = \frac{\Delta\omega_a^2}{\Delta\omega_a^2 + \omega_{1, \text{hard}}^2}$ is the square of the cosine of the angle

between the z -axis and the effective field relative to the water pool. Likewise, below, we use

$$\sin^2 \theta_a = \frac{\omega_{1, \text{hard}}^2}{\Delta\omega_a^2 + \omega_{1, \text{hard}}^2}, \quad \cos^2 \theta_b = \frac{\Delta\omega_b^2}{\Delta\omega_b^2 + \omega_{1, \text{hard}}^2} \quad \text{and} \quad \sin^2 \theta_b = \frac{\omega_{1, \text{hard}}^2}{\Delta\omega_b^2 + \omega_{1, \text{hard}}^2}.$$

The derived rates are:

$$R_{2\rho, b} = k_b + R_{2b} - \frac{1}{2} \sin^2 \theta_b (R_{2b} - R_{1b}) \quad (7)$$

$$\omega_{\text{eff}, b} = \sqrt{\omega_{1, \text{hard}}^2 + \Delta \omega_b^2} \quad (8)$$

$$R_{1\rho} = R_{1a} \cos^2 \theta_a + R_{2a} \sin^2 \theta_a + R_{\text{ex}} \quad (9)$$

$$R_{1\rho, \text{fast}} = R_{1b} \cos^2 \theta_b + R_{2b} \sin^2 \theta_b + k_b \quad (10)$$

$$R_{\text{ex}} = f_b \left(k_b \frac{\delta \omega_b^2}{\omega_{1, \text{hard}}^2 + \Delta \omega_a^2} \frac{\omega_{1, \text{hard}}^2}{\Gamma^2/4 + \Delta \omega_b^2} + R_{2b} \frac{\omega_{1, \text{hard}}^2}{\Gamma^2/4 + \Delta \omega_b^2} + k_b \sin^2 \theta_a \frac{R_{2b}(R_{2b} + k_b)}{\Gamma^2/4 + \Delta \omega_b^2} \right)$$

(11)

$$\Gamma = 2 \sqrt{\frac{R_{2b} + k_b}{k_b} \omega_{1, \text{hard}}^2 + (R_{2b} + k_b)^2}. \quad (12)$$

It should be noted that these rates are given (and used below) without assuming $\omega_a \rightarrow \infty$ (as was used in deriving Equation 3) or $\omega_b \rightarrow 0$ (as was used in deriving Equation 4).

2.3 | Interpretation of $R_{1\rho, \text{pul}}$

The first two terms of $R_{1\rho, \text{pul}}$ in Equation 3 describe saturation effects (that match previous results^{12,13}), and the last term describes transferred solute rotation effects (and are new results). The saturation effects are a weighted average of what the rotating frame longitudinal relaxation rate would be under CW irradiation ($R_{1\rho}$) and R_{1a} , with weighting factors corresponding to relaxation during and between pulses, respectively. The net effect is the sum of R_{1a} and direct saturation and transferred saturation terms:

$$R_{1\rho}^{\text{DC}_{\text{hard}}} + R_{1a}(1 - \text{DC}_{\text{hard}}) = R_{1a} + \underbrace{\frac{(R_{2a} - R_{1a})\text{DC}_{\text{hard}}\omega_{1, \text{hard}}^2}{\omega_{1, \text{hard}}^2 + \Delta \omega_a^2}}_{\text{direct saturation}} + \underbrace{\frac{\text{DC}_{\text{hard}}R_{\text{ex}}}{\text{transferred saturation}}}_{\text{transferred saturation}}. \quad (13)$$

The direct saturation term is a function of the water pool characteristics (and the pulse sequence) and is independent of the exchanging b-pool. It should be noted that the direct saturation is a function of the average irradiation power, $DC_{\text{hard}}\omega_{1,\text{hard}}^2 = DC\overline{\omega_1^2}$, as long as $\omega_{1,\text{hard}}^2 \ll \omega_a^2$, which is typically true when imaging amide exchange and probably true when imaging amine/hydroxyl exchange at higher fields. This sole dependence of the direct saturation on the average irradiation power is the basis of the CERT approach to imaging exchange.⁷ The transferred saturation term is proportional to the solute pool size (f_b), as can be seen in Equation 11. Although a full explanation of each term in R_{ex} is given elsewhere,¹⁵ the first term typically dominates and is proportional to the exchange rate k_b , with peaks at the water and solute resonances, and represents the contribution of solute exchange to water saturation under CW irradiation.

The last term in $R_{1\rho,\text{pul}}$ in Equation 3 describes the transfer of rotated solute magnetization to the measured water magnetization. This effect is proportional to the size of the solute pool (f_b), the rate of rotation pulses [$1/(t_p + t_d)$] and the normalized effect of a single solute rotation pulse on the water z -magnetization after damping and transfer.

The concept of solute labeling efficiency has been used previously to simplify and interpret analytic CEST results under CW irradiation.^{5,15,16} It is defined⁵ as the ratio of the contribution to $R_{1\rho}$ from exchange to the maximum possible contribution to $R_{1\rho}$ from exchange, when applying irradiation at the solute resonance and ignoring direct water effects. This leads to the maximum possible rate contribution from exchange:

$$R_{\text{ex}}^{\text{max}} \approx k_a \omega_1^2 / (\omega_1^2 + k_b^2 + k_b R_{2b}) = k_a \times \text{label efficiency},$$

which can, in theory, be measured using the AREX metric. (In practice, such isolation of exchange contributions using typical AREX approaches is not possible because of direct water effects and contributions from confounding exchanging pools to the reference scan acquired at the frequency on the opposite side of the water resonance.) This labeling efficiency approach can be extended to pulsed saturation when the pulses are long, and no rotation effects are included.^{12,13} In this no-rotation case, the labeling efficiency is multiplied by DC_{hard} , as this factor scales the first term in $R_{1\rho,\text{pul}}$ in Equation 4. However, further extending the labeling efficiency concept to include rotation contributions to $R_{1\rho,\text{pul}}$ leads to a less informative analytic form, as these contributions scale with the pulse rate $1/(t_p + t_d)$, and not the exchange rate k_a , as can be seen in the third term in Equation 4. Nonetheless, it should be noted that, as the rotation terms can be greater than zero, they can conceivably add to the solute labeling beyond that which is possible with CW irradiation.

2.4 | Comparisons between analytic results and numerical integration

In order to illustrate the effect of exchange on the signal, and to clarify the regimes in which the analytic solutions are accurate, all the plots in this article examine the results under nine conditions: three solute conditions and three irradiation powers. The plot rows correspond to no exchange ($k_b = 0.0001 \text{ s}^{-1}$, $\omega_b - \omega_a = 3.5 \text{ ppm}$), amide exchange ($k_b = 50 \text{ s}^{-1}$, $\omega_b - \omega_a = 3.5 \text{ ppm}$) and amine exchange ($k_b = 1000 \text{ s}^{-1}$, $\omega_b - \omega_a = 2.0 \text{ ppm}$). The plot columns correspond to differing B_1 amplitudes (for the CW simulations) or to differing roots of the mean square B_1 amplitudes (for the pulsed irradiation simulations), as indicated in the

plot. All of the plots use $f_b = 0.004$, $R_{1a} = 1 \text{ s}^{-1}$, $R_{1b} = 1 \text{ s}^{-1}$, $R_{2a} = 10 \text{ s}^{-1}$, $R_{2b} = 100 \text{ s}^{-1}$ and $B_0 = 9.4 \text{ T}$. (All of the results presented in this article have been tested only under these nine conditions, and any application outside of this regime should be separately tested against numerical integration.) The Matlab code (including all underlying calculations) used to generate these figures, together with the Mathematica code for Equations 3, 4, 17 and 24–28, are available for download at <https://github.com/gochberg/towards-analytic-pulsed-CEST>.

Figure 2 compares the analytic solution for the measured water signal ($Z_a^{\text{ss, pul}}$, Equations 1–3 and 5–12) with numerical results of integrating the coupled Bloch equations over the corresponding pulse train (using Matlab R2016b, Mathworks, Natick, MA, USA) at a range of irradiation frequencies. (Although the derivation of Equation 3 assumed $\omega_a \rightarrow \infty$, the derivations underlying Equations 5–12 made no such assumption. Hence direct saturation effects still exist at small ω_a values.) The comparisons are performed using a pulse flip angle ($\alpha = \omega_{1,\text{avg}} t_p$) of 180° , three average irradiation powers (0.6, 1.8 and $3.6 \mu\text{T}$) and three pulse widths (t_p of 20, 6.66 and 3.33 ms, respectively), chosen so that the values of $\omega_{1,\text{hard}}$ (1, 3 and $6 \mu\text{T}$) match the CW cases examined below. It should be noted that the analytic solution matches numerical results for the no-exchange and amide cases at the solute resonance (3.5 ppm), but matches for fast-exchanging amines (at 2.0 ppm) only at lower irradiation powers. Under all conditions, the analytic solution does not match numerical results close to the water resonance ($\omega_a = 0$), which follows directly from the derivation below, where direct water magnetization rotation is ignored.

Figure 3 compares the analytic solutions for $Z_a^{\text{ss, pul}}$ at the solute resonance (Equations 1, 2 and 4–12) with numerical results as a function of the flip angle α . This plot illustrates the core advancement in this work: the ability to analytically approximate the effect of solute rotations on the steady-state water signal. The irradiations are performed using a constant t_p (16.8, 5.6 and 2.8 ms for the three powers) and with varying t_d values (0.4–194.5, 0.1–64.8 and 0.1–32.4 ms, respectively) chosen such that the irradiation power is constant as α varies. (A different pulse width t_p is necessary at each power level in order to span the same range of angles α .) The strong agreement between the analytic and numerical results for amide exchange at all irradiation powers should be noted, whereas the results for amine exchange (especially at high powers) indicate inaccuracies in the analytic results. Given the wide acceptance of the coupled Bloch equations as an accurate model for two-pool systems, these comparisons of analytic results with numerical integrations are sufficient to establish validity. Nonetheless, for completeness, we also compare analytic predictions with experimental measures in a two-pool creatine phantom in the Appendix (Section A1).

2.5 | Derivation

The derivation of the analytic solution is broken into two distinct parts. First, the six coupled Bloch equations are approximately solved for the z -magnetizations in the CW case with initial conditions restricted to arbitrary values along the z -axis. (We only solve for the z -magnetizations of the a and b pools, as we are ultimately interested in modeling a pulse sequence that has spoilers between irradiation pulses.) Second, the analytic solution of the water pool after repeated irradiation by off-resonant shaped pulses is approximated by repeated irradiation by corresponding square pulses, each of which has the same integrated

amplitude and power as the shaped pulse. (DC_{hard} and $\omega_{1,\text{hard}}$ come from matching both the average amplitude and power, i.e. amplitude squared, of the train of shaped pulses, which was motivated by the desire to induce similar rotation effects, which are proportional to amplitude, and saturation effects, which are proportional to amplitude squared.) The square-pulse irradiation is then step-wise solved during irradiation and free recovery, and the steady state is defined as the magnetization that remains constant after a pulse/recovery repetition.

2.5.1 | Solution under CW irradiation—Under CW irradiation, the evolution of the water (pool a) and solute (pool b) magnetizations is governed by:

$$\frac{d}{dt} \begin{bmatrix} X_a \\ Y_a \\ Z_a \\ X_b \\ Y_b \\ Z_b \end{bmatrix} = \begin{bmatrix} -R_{2a} - k_a & \Delta\omega_a & 0 & k_a & 0 & 0 \\ -\Delta\omega_a & -R_{2a} - k_a & \omega_1 & 0 & k_a & 0 \\ 0 & -\omega_1 & -R_{1a} - k_a & 0 & 0 & k_a \\ k_b & 0 & 0 & -R_{2b} - k_b & \Delta\omega_b & 0 \\ 0 & k_b & 0 & -\Delta\omega_b & -R_{2b} - k_b & \omega_1 \\ 0 & 0 & k_b & 0 & -\omega_1 & -R_{1b} - k_b \end{bmatrix} \begin{bmatrix} X_a \\ Y_a \\ Z_a \\ X_b \\ Y_b \\ Z_b \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ R_{1a} \\ 0 \\ 0 \\ R_{1b} \end{bmatrix} \quad (14)$$

where $Z_a \equiv M_{za}/M_{0a}$, $Z_b \equiv M_{zb}/M_{0b}$ and, likewise, for X_a , Y_a , X_b and Y_b . This equation adopts the notation of Zaiss and Bachert,¹⁵ except with Z_a instead of Z (to clarify the pool), a correction to the sign of the ω terms in the coupling matrix (to make B_0 along the $+z$ axis and B_1 along the $+x$ axis) and the use of normalized magnetization. The solution can be written in matrix form (as shown below), but there is no analytic solution for the corresponding sixth-order characteristic equation. However, numerical results (examined below) make clear that the six rates correspond to two exponential recoveries ($R_{1\rho}$ and what we will call $R_{1\rho,\text{fast}}$) and two sets of complex conjugate eigenvalues corresponding to damped cosine and sine terms oscillating at the effective precession rates of the a- and b-pools. In addition to determining these rates, an analytic solution would need to solve for six corresponding amplitudes (which are functions of the initial conditions) and steady-state values for each of the two pools. We solve for all six rates and some of the amplitudes below in order to find a relatively simple approximate solution.

For the water pool, we take the solution from Zaiss and Bachert⁵ and modify it by removing any discrete jumps at $t = 0$:

$$Z_a(t) = \left(Z_a^i - Z_a^{\text{ss,cw}} \right) e^{-R_{1\rho} t} + Z_a^{\text{ss,cw}} \quad (15)$$

$$Z_a^{ss,cw} = \cos^2 \theta_a \frac{R_{1a}}{R_{1\rho}} \quad (16)$$

where Z_a^i is the initial value at $t=0$ and the superscript 'ss, cw' indicates the steady-state value under CW irradiation. This solution only uses the slowest rate ($R_{1\rho}$) and ignores the additional rates relevant during short irradiation times, which (assuming a small b-pool) make only small contributions to the water pool magnetization dynamics, except when small offsets facilitate direct water rotation. We ignore this direct water rotation as solving for the water rotation in the CW case would provide little insight into the solution under shaped pulsed irradiation, where the water rotation is dramatically affected by the pulse shape and, in the general case, has no known analytic solution. (This is a problematic issue. The discrete jump at $t=0$ seen in previous results⁵ comes from using an amplitude for the rotation component that approximates the square pulse case while assuming an infinitely fast decay rate for this component. Neither the shape or rate assumptions are warranted in the shaped and short pulse conditions examined here. However, our approach of ignoring these rotation components also produces inaccuracies, which are discussed below).

The solution for the solute pool is more complex, and is broken into two parts, each of which reduces the problem from six dimensions to three. At long times, the steady-state solution of the b-pool can be solved algebraically by setting the derivative to zero and assuming the a-pool is at its steady-state value along the effective field, with $Z_a = Z_a^{ss, cw}$ (Equation 16), $X_a = Z_a^{ss, cw} \sin \theta_a / \cos \theta_a$ and $Y_a = 0$. This gives:

$$Z_b^{ss,cw} = \frac{Z_a^{ss,cw} k_b \left(\frac{\Delta \omega_b}{\Delta \omega_a} \omega_{1, \text{hard}}^2 + \Delta \omega_b^2 + (R_{2b} + k_b)^2 \right) + R_{1a} \left(\Delta \omega_b^2 + (R_{2b} + k_b)^2 \right)}{(R_{2b} + k_b) \omega_{1, \text{hard}}^2 + (R_{1b} + k_b) \left(\Delta \omega_b^2 + (R_{2b} + k_b)^2 \right)}. \quad (17)$$

At short times, the rates and amplitudes of $R_{1\rho, \text{fast}}$ and damped oscillatory components (with rates labeled as $R_{2\rho, b}$ and $\omega_{\text{eff}, b}$) can be determined by assuming that the a-pool magnetization is constant and equal to the projection of the initial magnetization along the effective field of the a-pool. This value comes from assuming that the rate of change of the solute pool normalized magnetization is fast relative to $R_{1\rho}$ -induced changes in the normalized water pool magnetization (which can hence be ignored) and slow relative to the water magnetization precession dynamics (which oscillate at rate $\omega_{\text{eff}, a}$), and which can hence be averaged. Figure 4 supports these assertions by plotting the numerically determined time dependence of $Z_a(t)$ and $Z_b(t)$, together with the projection of Z_a^i along the effective field.

This assumption (valid at short times) that the a-pool magnetization lies along its effective field leads to the coupled equations:

$$\frac{d}{dt} \begin{bmatrix} X_b \\ Y_b \\ Z_b \end{bmatrix} = \begin{bmatrix} -R_{2b} - k_b & \Delta\omega_b & 0 \\ -\Delta\omega_b & -R_{2b} - k_b & \omega_1 \\ 0 & -\omega_1 & -R_{1b} - k_b \end{bmatrix} \begin{bmatrix} X_b \\ Y_b \\ Z_b \end{bmatrix} + \begin{bmatrix} \frac{k_b \Delta\omega_a \omega_1 Z_a^i}{\omega_1^2 + \Delta\omega_a^2} \\ 0 \\ \frac{k_b \Delta\omega_a^2 Z_a^i}{\omega_1^2 + \Delta\omega_a^2} + R_{1b} \end{bmatrix}. \quad (18)$$

It should be noted that this 3×3 evolution matrix is identical to the evolution matrix in the uncoupled Bloch equations, but with $R_{1b} \rightarrow R_{1b} + k_b$ and $R_{2b} \rightarrow R_{2b} + k_b$. Hence, the eigenvalues of this matrix (which dictate the evolution rates) can be determined by making these substitutions into previously determined solutions of the Bloch equations, either exact¹⁷ or approximate.¹⁸ We use the approximate solutions to keep the final analytic result as simple as possible. The results for $R_{2\rho,b}$ and $\omega_{\text{eff},b}$ are given in Equations 7 and 8 above, and the value for $R_{1\rho,\text{fast}}$ is:

$$R_{1\rho,\text{fast}} = \frac{R_{2b} + R_{1b} \left(\frac{\Delta\omega_b}{\omega_{1,\text{hard}}} \right)^2}{1 + \left(\frac{\Delta\omega_b}{\omega_{1,\text{hard}}} \right)^2} + k_b = R_{1b} \cos^2 \theta_b + R_{2b} \sin^2 \theta_b + k_b. \quad (19)$$

Even though we only include $R_{1\rho}$ evolution for the a-pool, for completeness we guess that $R_{2\rho,a}$ and $\omega_{\text{eff},a}$ have a form similar to the b-pool rates:

$$R_{2\rho,a} = k_a + R_{2a} - \frac{1}{2} \sin^2 \theta_a (R_{2a} - R_{1a}) \quad (20)$$

$$\omega_{\text{eff},a} = \sqrt{\omega_{1,\text{hard}}^2 + \Delta\omega_a^2}. \quad (21)$$

Figure 5 compares all the analytic rate equations to numerically determined eigenvalues of the 6×6 evolution matrix in Equation 14. The strong agreement should be noted. It should also be noted that this is the first presentation (that we know of) of analytic approximations of all six eigenvalues (including, most notably, $R_{2\rho,a}$). Finally, it should also be noted that, in general, both the a-pool and b-pool evolve at all six rates, and that the subscripts 'a' and 'b' in the rates correspond to the expected relative amplitudes of these six components, e.g. the a-pool has a much larger component that precesses at angular rate $\omega_{\text{eff},a}$ than at $\omega_{\text{eff},b}$.

The determination of the component amplitudes for the b-pool is more complex than finding the rates. The amplitude of the decaying oscillatory (with rates $R_{2\rho,b}$ and $\omega_{\text{eff},b}$) and rapid exponential (with rate $R_{1\rho,\text{fast}}$) components can be solved using the short-time approximation (Equation 18) and a Laplace transform approach, as in Morris and Chilvers.¹⁷

The derivation is outlined in the Appendix (Section A2). In contrast with Morris and Chilvers,¹⁷ we use the approximate rates listed above when calculating the amplitude values to simplify the final result. The decaying oscillatory components of the b-pool corresponding to precession about the a-pool effective field (with rates $R_{2\rho,a} \pm i\omega_{\text{eff},a}$) are ignored in this work and the corresponding amplitudes are set to zero. Finally, the amplitude of the $R_{1\rho}$ component can be solved by using the relations at $t = 0$ between the b-pool initial value (Z_b^i), the steady-state value and the component amplitudes. The results are:

$$Z_b(t) = c_b^{R_{1\rho}} e^{-R_{1\rho}t} + c_b^{R_{1\rho, \text{fast}}} e^{-R_{1\rho, \text{fast}}t} + c_b^{\cos, \omega_{\text{eff},b}} e^{-R_{2\rho,b}t} \cos(\omega_{\text{eff},b}t) + c_b^{\sin, \omega_{\text{eff},b}} e^{-R_{2\rho,b}t} \sin(\omega_{\text{eff},b}t) + Z_b^{\text{ss}, \text{cw}} \quad (22)$$

$$c_b^{R_{1\rho}} = Z_b^i - c_b^{R_{1\rho, \text{fast}}} - c_b^{\cos, \omega_{\text{eff},b}} - Z_b^{\text{cw}, \text{ss}} \quad (23)$$

$$c_b^{R_{1\rho, \text{fast}}} = -Z_a^i \frac{k_b}{k} \left(\frac{\omega_{1, \text{hard}}^2}{(\omega_{1, \text{hard}}^2 + \Delta\omega_a^2)} \Delta\omega_a \Delta\omega_b + \frac{\Delta\omega_a^2}{(\omega_{1, \text{hard}}^2 + \Delta\omega_a^2)} \left(\Delta\omega_b^2 + (R_{2b} + k_b - R_{1\rho, \text{fast}})^2 \right) \right) + Z_b^i \frac{R_{1\rho, \text{fast}}}{k} \left(\Delta\omega_b^2 + (R_{2b} + k_b - R_{1\rho, \text{fast}})^2 \right) - \frac{R_{1b}}{k} \left(\Delta\omega_b^2 + (R_{2b} + k_b - R_{1\rho, \text{fast}})^2 \right) \quad (24)$$

$$c_b^{\cos, \omega_{\text{eff},b}} = Z_b^i - Z_a^i \frac{\Delta\omega_a k_b (\omega_{1, \text{hard}}^2 \Delta\omega_b + \Delta\omega_a (\Delta\omega_b^2 + (R_{2b} + k_b)^2))}{(\omega_{1, \text{hard}}^2 + \Delta\omega_a^2) (\omega_{1, \text{hard}}^2 (R_{2b} + k_b) + (R_{1b} + k_b) (\Delta\omega_b^2 + (R_{2b} + k_b)^2))} - \frac{R_{1b} (\Delta\omega_b^2 + (R_{2b} + k_b)^2)}{\omega_{1, \text{hard}}^2 (R_{2b} + k_b) + (R_{1b} + k_b) (\Delta\omega_b^2 + (R_{2b} + k_b)^2)} - c_b^{R_{1\rho, \text{fast}}} \quad (25)$$

$$c_b^{\sin, \omega_{\text{eff},b}} = \frac{1}{\omega_{\text{eff},b}} \left(Z_a^i \frac{\Delta\omega_a^2}{\omega_{1, \text{hard}}^2 + \Delta\omega_a^2} k_b - Z_b^i (R_{1b} + k_b) + R_{1b} + R_{1\rho, \text{fast}} c_b^{R_{1\rho, \text{fast}}} + R_{2\rho,b} c_b^{\cos, \omega_{\text{eff},b}} \right) \quad (26)$$

$$k = R_{1\rho, \text{fast}} \left((R_{2\rho, \text{b}} - R_{1\rho, \text{fast}})^2 + \omega_{\text{eff, b}}^2 \right). \quad (27)$$

2.5.2 | CW solutions: analytic versus numerical—The accuracy of these analytic solutions for component amplitudes can be checked by comparisons with the numerical solutions, which are calculated as described in the Appendix (Section A3). The results are plotted as a function of the irradiation frequency in Figure 6 for the a-pool (Equations 15 and 16) and in Figure 7 for the b-pool (Equations 17 and 23–27). The reasonable agreement should be noted, as long as there is limited direct water (a-pool) rotation, which has been ignored in our analytic form. We have also ignored $R_{1\rho, \text{fast}}$ and $\omega_{\text{eff, b}}$ contributions to the a-pool, together with $\omega_{\text{eff, a}}$ contributions to the b-pool, all of which appear to give relatively small contributions. A similar agreement can be seen in Figures 8 (a-pool) and 9 (b-pool), where we include the time-dependent terms in Equations 15 and 22, respectively, and plot as a function of time when applying irradiation at the solute resonance. It should be noted that most of the discrepancies between the analytic and numerical results occur in the subplots in the bottom right-hand corner, where higher irradiation powers, smaller solute resonance offsets and higher exchange rates occur.

2.5.3 | Solution under pulsed irradiation—There are two steps to go from the above solution for CW irradiation to the solution for pulsed irradiation. First, we approximate irradiation with shaped pulses by irradiation with square pulses, whilst constraining the integrals of the field amplitude B_1 and the field amplitude squared B_1^2 to be the same for the two sequences. These constraints are designed to keep the induced rotation (a function integrated B_1) and saturation (a function integrated B_1^2) the same for the two pulse sequences. These constraints fully specify the square pulse duration and amplitude, and have the added benefit of not requiring additional calibration measurements or limits on the pulse shape, as in previous work.¹³ However, they ignore adiabatic effects that occur during shaped pulses that have slowly varying amplitudes (e.g. Gaussian shapes), which may be a significant source of error for the analytic solutions in this work, as discussed below. The resulting relationships between the pulse durations (t_p and $t_{p, \text{hard}}$), pause durations (t_d and $t_{d, \text{hard}}$), duty cycles (DC and DC_{hard}) and amplitudes ($\omega_{1, \text{avg}}$ and $\omega_{1, \text{hard}}$) are given in Equations 5 and 6 above and are illustrated in Figure 1b.

The second step in the derivation of the pulsed analytic solution is to connect the CW solution during $t_{p, \text{hard}}$ to the free recovery solution during $t_{d, \text{hard}}$, which has the same form as the biexponential solution utilized in quantitative MT experiments.^{19,20} The steady-state solution is found by equating the result before and after a pause-pulse repetition, an approach employed in previous work.^{12,21} This calculation is outlined in the Appendix (Section A4). The resulting solution is too long to be useful. Instead, a Taylor series approximation is made (with help from Mathematica v10.4.0) to zeroth order in the unitless small parameters t_b , $R_{1a}t_{d, \text{hard}}$, $R_{1\rho}t_{p, \text{hard}}$, $R_{1b}/\omega_{1, \text{hard}}$ and $R_{2b}/\omega_{1, \text{hard}}$. (As an aside, it should be noted that we treat all these parameters as equally small, which is certainly not always justified for $R_{2b}/\omega_{1, \text{hard}}$. Nonetheless, we found this approximation to be necessary to simplify the final analytic solution, and an algebraically simple solution is our ultimate goal.

Comparisons with numerical results show that this solution is still relatively robust, even though $R_{2b}/\omega_{1,\text{hard}}$ is as large as 0.37 (at the lowest average power) in Figure 2 and 0.47 (at the smallest angle and lowest average power) in Figure 3.)

The resulting steady-state water magnetization comes from Equations 1, 2 and:

$$\begin{aligned}
 R_{1\rho,\text{pul}} &= R_{1\rho}\text{DC}_{\text{hard}} + R_{1a}(1 - \text{DC}_{\text{hard}}) \\
 &+ \frac{1}{(t_p + t_d)} \frac{f_b(1 - e^{-k_b t_d, \text{hard}})}{(\omega_{1,\text{hard}}^2 + \Delta\omega_b^2 + k_b^2)(\omega_{1,\text{hard}}^2 + \Delta\omega_a^2)} \\
 &\times \frac{1}{1 - e^{-k_b t_d, \text{hard}} - R_{2\rho, b} t_p, \text{hard}} \cos(\omega_{\text{eff}, b} t_p, \text{hard}) + \frac{\Delta\omega_b^2}{\omega_{1,\text{hard}}^2} (1 - e^{-k_b t_d, \text{hard}} - R_{1\rho, \text{fast}} t_p, \text{hard}) \\
 &\times \left[\Delta\omega_a^2(\omega_{1,\text{hard}}^2 + \Delta\omega_b^2) - \Delta\omega_a \Delta\omega_b \left(\omega_{1,\text{hard}}^2 + \Delta\omega_b^2 + k_b^2 \right) \left(1 - e^{-R_{1\rho, \text{fast}} t_p, \text{hard}} \right) - k_b^2 \right] \\
 &+ \left(\omega_{1,\text{hard}}^2 + \Delta\omega_b^2 + k_b^2 \right) \left(\omega_{1,\text{hard}}^2 \Delta\omega_b^2 \left(1 - e^{-R_{1\rho, \text{fast}} t_p, \text{hard}} \right) - \right. \\
 &\left. e^{-R_{2\rho, b} t_p, \text{hard}} \left(\Delta\omega_a^2(\omega_{1,\text{hard}}^2 + \Delta\omega_b^2) + \Delta\omega_a \Delta\omega_b k_b^2 + \omega_{1,\text{hard}}^2 (\omega_{1,\text{hard}}^2 + \Delta\omega_b^2 + k_b^2) \right) \right. \\
 &\left. \left(\cos(\omega_{\text{eff}, b} t_p, \text{hard}) - e^{-R_{2\rho, b} t_p, \text{hard}} \Delta\omega_a \left(\Delta\omega_a - \Delta\omega_b \right) k_b \sqrt{\omega_{1,\text{hard}}^2 + \Delta\omega_b^2} \sin(\omega_{\text{eff}, b} t_p, \text{hard}) \right) \right]
 \end{aligned}
 \tag{28}$$

The form simplifies if we assume that the irradiation is applied very far from the water resonance (Equation 3) and when also irradiating at the solute resonance (Equation 4).

3 | DISCUSSION

We have presented here an analytic solution to pulsed CEST and CERT sequences that includes both saturation and rotation effects and which is largely accurate for amides at high fields. As such, the results may be used to evaluate the underlying parameter dependence of novel CEST metrics and may be especially useful in assessing claims of biometric specificity. However, caution is warranted when applying to tissue studies as the analytic results are: (1) based on a two-pool model; and (2) less accurate at the higher exchange rates, lower offsets and, typically, higher irradiation powers of amines. The first issue is likely to be addressed by linearly summing the many contributions to $R_{1\rho}$ in tissue, although we have not demonstrated this. The second issue reflects multiple possible sources of error.

3.1 | Sources of error

In deriving the relatively simple final results in Equations 1–4 and 28 (together with the corresponding rates in Equations 7–12), we made many approximations, making the dominant source of error unclear. Approximations include: (1) dropping higher order terms from the Taylor series of both the CW rates (following Torrey's approach) and the pulsed irradiation steady state; (2) the absence of several eigen-components in the CW solution, most notably the water rotation terms; and (3) the inherent problem with using one pulse sequence (a train of square pulses) as a proxy for another (a train of shaped pulses). The first of these approximations was briefly discussed above, and will be skipped here. The second approximation causes clear discrepancies between the analytic approximation and the numerical integration at low offsets and high irradiation fields, which is especially clear when approaching the lower right-hand corner in Figures 3 and 8. The third approximation causes the most complex discrepancies, as [unlike discrepancies caused by approximations (1) and (2)] they do not clearly correspond to missing additive terms.

Using a train of square pulses (to approximate a train of shaped pulses) results in spectral shape and adiabaticity differences. Although the Fourier relationship between a pulse shape and the frequency response is only strictly true at low angles, the sinc shape (which is the Fourier transform of a square pulse) is apparent in the analytic solution for amide exchange at 1.8 μ T in Figure 2. A more subtle issue related to pulse shape is the role of adiabaticity. Adiabatic effects happen in every shaped pulse, not only those that are explicitly designed to be adiabatic. Any time the direction of the effective field changes gradually, as it does when applying a Gaussian pulse off-resonance, some portion of the magnetization will adiabatically follow the effective field. However, a square pulse changes amplitude instantaneously, causing discrete jumps in the direction of the effective field and precluding adiabatic effects. This dependence on pulse shape is apparent in Figure 10, which plots the z -magnetizations of the water and solute pools during two pulse repetition periods when applying irradiation at the solute resonance. Although the numerical and analytic results match well for the no-exchange and amide regimes, large deviations are clear during amine exchange. The adiabatic source for this deviation is most clear for $Z_a(t)$ for amine exchange

at high B_1 (lower right plot), where the Gaussian shape of the numerical/analytic deviation is apparent. These adiabatic contributions are magnified and extend to amides when applying irradiation off-resonance relative to the solute (results not shown), as the effective field relative to the solute changes direction during the pulse in this case.

3.2 | Comparisons with previous analytic solutions

Although there have been several approximate solutions for pulsed saturation,^{10,12,16,21} the most complete and closest to the present work is by Meissner et al.¹³ The first two terms in Equation 4 match equation 11 in Meissner et al.,¹³ at least in the case of $\omega_b = 0$ and the water effective field direction $\theta = 0$. They derive the analytic form for the direct and transferred saturation effects by analytically integrating $R_{1\rho}$ for the special case when $\omega_1(t)$ is Gaussian. In contrast, as we wish to capture rotation transfer effects (in addition to direct and transferred saturation effects), we mimic the shaped pulse by a hard pulse with the same integrated ω_1^2 (to capture $R_{1\rho}$ saturation) and ω_1 (to capture rotation effects). (Unlike Meissner et al.,¹³ we also include rotation and fast exponential terms and include non-zero ω_b and non-infinite ω_a .) These rotation effects produce the third term in Equation 4 (and Equations 3 and 28), which does not appear in Meissner et al.¹³

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Abbreviations used

CERT	chemical exchange rotation transfer
CEST	chemical exchange saturation transfer
CW	continuous wave
DC	duty cycle of shaped pulse train
f_b	b-pool size relative to a-pool size
k_a	exchange rate from a-pool to b-pool
k_b	exchange rate from b-pool to a-pool
MT	magnetization transfer
$R_{1\rho}, R_{2\rho}$	relaxation rates in the rotating frame
t_p	shaped pulse duration
t_d	duration between shaped pulses
X_a, Y_a, Z_a	normalized magnetization components of a-pool
X_b, Y_b, Z_b	normalized magnetization components of b-pool

References

1. Zhou J, Lal B, Wilson DA, Laterra J, van Zijl PCM. Amide proton transfer (APT) contrast for imaging of brain tumors. *Magn Reson Med*. 2003; 50:1120–1126. [PubMed: 14648559]
2. Zhou J, Payen J-F, Wilson DA, Traystman RJ, van Zijl PCM. Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. *Nat Med*. 2003; 9:1085–1090. [PubMed: 12872167]
3. Haris M, Nanga RPR, Singh A, et al. Exchange rates of creatine kinase metabolites: feasibility of imaging creatine by chemical exchange saturation transfer MRI. *NMR Biomed*. 2012; 25:1305–1309. [PubMed: 22431193]
4. Walker-Samuel S, Ramasawmy R, Torrealdea F, et al. In vivo imaging of glucose uptake and metabolism in tumors. *Nat Med*. 2013; 19:1067–1072. [PubMed: 23832090]
5. Zaiss M, Bachert P. Exchange-dependent relaxation in the rotating frame for slow and intermediate exchange – modeling off-resonant spin-lock and chemical exchange saturation transfer. *NMR Biomed*. 2013; 26:507–518. [PubMed: 23281186]
6. Jin T, Wang P, Zong X, Kim S-G. Magnetic resonance imaging of the Amine-Proton EXchange (APEX) dependent contrast. *Neuroimage*. 2012; 59:1218–1227. [PubMed: 21871570]
7. Zu Z, Janve VA, Xu J, Does MD, Gore JC, Gochberg DF. A new method for detecting exchanging amide protons using chemical exchange rotation transfer. *Magn Reson Med*. 2012; 69:637–647. [PubMed: 22505325]
8. Zu Z, Janve VA, Li K, Does MD, Gore JC, Gochberg DF. Multi-angle ratiometric approach to measure chemical exchange in amide proton transfer imaging. *Journal*. 2012; 68:711–719.
9. Zu Z, Xu J, Li H, et al. Imaging amide proton transfer and nuclear Overhauser enhancement using chemical exchange rotation transfer (CERT). *Journal*. 2014; 72:471–476.
10. Zhou J, Wilson DA, Sun PZ, Klaus JA, van Zijl PCM. Quantitative description of proton exchange processes between water and endogenous and exogenous agents for WEX, CEST, and APT experiments. *Journal*. 2004; 51:945–952.
11. Chappell MA, Donahue MJ, Tee YK, et al. Quantitative Bayesian model-based analysis of amide proton transfer MRI. *Magn Reson Med*. 2012; 70:556–567. [PubMed: 23008121]
12. Roeloffs V, Meyer C, Bachert P, Towards ZM. quantification of pulsed spinlock and CEST at clinical MR scanners: an analytical interleaved saturation–relaxation (ISAR) approach. *NMR Biomed*. 2015; 28:40–53. [PubMed: 25328046]
13. Meissner JE, Goerke S, Rerich E, et al. Quantitative pulsed CEST-MRI using Ω -plots. *NMR Biomed*. 2015; 28:1196–1208. [PubMed: 26278686]
14. Zu Z, Li K, Janve VA, Does MD, Gochberg DF. Optimizing pulsed-chemical exchange saturation transfer imaging sequences. *Magn Reson Med*. 2011; 66:1100–1108. [PubMed: 21432903]
15. Zaiss M, Bachert P. Chemical exchange saturation transfer (CEST) and MR Z-spectroscopy in vivo: a review of theoretical approaches and methods. *Phys Med Biol*. 2013; 58:R221–R269. [PubMed: 24201125]
16. Sun PZ, van Zijl PCM, Zhou J. Optimization of the irradiation power in chemical exchange dependent saturation transfer experiments. *J Magn Reson*. 2005; 175:193–200. [PubMed: 15893487]
17. Morris GA, Chilvers PB. General analytical solutions of the Bloch equations. *J Magn Reson Ser A*. 1994; 107:236–238.
18. Torrey H. Transient nutations in nuclear magnetic resonance. *Phys Rev*. 1949; 76:1059–1068.
19. Edzes HT, Samulski ET. Cross relaxation and spin diffusion in proton NMR of hydrated collagen. *Nature*. 1977; 265:521–523. [PubMed: 834303]
20. Gochberg DF, Kennan RP, Gore JC. Quantitative studies of magnetization transfer by selective excitation and T1 recovery. *Magn Reson Med*. 1997; 38:224–231. [PubMed: 9256101]
21. Santyr GE, Fairbanks EJ, Kelcz F, Sorenson JA. Off-resonance spin locking for MR imaging. *Magn Reson Med*. 1994; 32:43–51. [PubMed: 8084236]
22. Gochberg DF, Kennan RP, Maryanski MJ, Gore JC. The role of specific side groups and pH in magnetization transfer in polymers. *J Magn Reson*. 1998; 131:191–198. [PubMed: 9571092]

23. Gochberg DF, Kennan RP, Robson MD, Gore JC. Quantitative imaging of magnetization transfer using multiple selective pulses. *Magn Reson Med*. 1999; 41:1065–1072. [PubMed: 10332891]

APPENDIX A

A1 | Analytic *versus* experimental results in a creatine phantom

Figure A1 plots $Z_a^{ss,pul}$ analytic results (dots, Equations 1, 2 and 4–12) *versus* experimental measures (lines) in a creatine phantom as a function of the B_1 -induced rotation angle when irradiating at the solute resonance ($\omega_b = 0$). The strong agreement should be noted, with the difference at all angles probably originating from the limited precision of experimental B_1 tuning. The creatine phantom is composed of 50mM creatine, 0.75mM $MnCl_2$, at pH 6.4. Sample parameters used in the analytic solution were determined by an inversion recovery experiment to determine R_{1a} (0.88 s^{-1}) and a CW irradiation CEST experiment using 38 offsets between -2000 and 2000 Hz , two normalizers with offsets of $100\,000\text{ Hz}$ and five powers ($0.25, 0.5, 1, 1.5$ and $2\text{ }\mu\text{T}$) to determine R_{2a} (11 s^{-1}), ω_a (10 s^{-1}), R_{2b} (72 s^{-1}), k_a (0.057 s^{-1}) and k_b (38 s^{-1}), with the constraint that $\omega_b = \omega_a + 1.9\text{ ppm}$ and $R_{1b} = R_{1a}$.

A2 | b-pool component amplitudes under CW irradiation

This section starts with Equation 18 and derives $c_b^{R_{1\rho, fast}}$, $c_b^{\cos, \omega_{eff, b}}$ and $c_b^{\sin, \omega_{eff, b}}$ following the approach of Morris and Chilvers¹⁷ and using Mathematica v10.4. Taking the Laplace transform of Equation 18 and replacing ω_1 with $\omega_{1, hard}$, as we are applying it to the case of CW irradiation, gives:

FIGURE A1.

$Z_a^{ss,pul}$ analytic results (dots, Equations 1, 2 and 4–12) *versus* experimental measures (lines) in a creatine phantom as a function of the B_1 -induced rotation angle when irradiating at the solute resonance ($\omega_b = 0$). Pulsed irradiation is applied with α between 150 and 420°, $t_p = 16.8$ ms and a root-mean-square B_1 amplitude of 0.6 μ T

$$\begin{bmatrix} p + R_{2b} + k_b & -\Delta\omega_b & 0 \\ \Delta\omega_b & p + R_{2b} + k_b & -\omega_{1,\text{hard}} \\ 0 & \omega_{1,\text{hard}} & p + R_{1b} + k_b \end{bmatrix} \begin{bmatrix} \tilde{X}_b \\ \tilde{Y}_b \\ \tilde{Z}_b \end{bmatrix} = \begin{bmatrix} Z_a^i \frac{k_b \Delta\omega_a}{\omega_{1,\text{hard}}^2 + \Delta\omega_a^2} \frac{1}{p} \\ 0 \\ \left(\frac{Z_a^i k_b \Delta\omega_a^2}{\omega_{1,\text{hard}}^2 + \Delta\omega_a^2} + R_{1b} \right) \frac{1}{p\omega_{1,\text{hard}}} + Z_b^i \end{bmatrix} \quad (\text{A1})$$

where ‘~’ indicates the Laplace transform of a variable, with transform variable p . Equation A1 can be solved algebraically and put in the form:

$$\begin{aligned} \tilde{Z}_b &= \frac{g(p)}{p\Delta(p)} \\ &= \frac{Z_a^i \frac{\Delta\omega_a \Delta\omega_b k_b \omega_{1,\text{hard}} + \Delta\omega_a^2 k_b}{\omega_{1,\text{hard}}^2 + \Delta\omega_a^2} + Z_b^i \left(\Delta\omega_b^2 + (k_b + R_{2b} + p)^2 \right) p + R_{1b} \left(\Delta\omega_b^2 + (k_b + R_{2b} + p)^2 \right)}{p\Delta(p)} \end{aligned} \quad (\text{A2})$$

$\Delta(p)$ is the determinant of the matrix in Equation A1:

$$\Delta(p) = (k_b + R_{1b} + p) \left(\Delta\omega_b^2 + (k_b + R_{2b} + p)^2 \right) + (k_b + R_{2b} + p) \omega_{1,\text{hard}}^2 \quad (\text{A3})$$

which can also be factored into its roots:

$$(p + R_{1\rho,\text{fast}}) \left[(p + R_{2\rho,\text{b}})^2 + \omega_{\text{eff},\text{b}}^2 \right]. \quad (\text{A4})$$

Hence, expanding $\tilde{Z}_b$ into partial fractions gives:

$$\tilde{Z}_b = \frac{c_b^{R_{1\rho,\text{fast}}}}{p + R_{1\rho,\text{fast}}} + \frac{c_b^{\cos, \omega_{\text{eff},\text{b}}} (p + R_{2\rho,\text{b}}) + c_b^{\sin, \omega_{\text{eff},\text{b}}} \omega_{\text{eff},\text{b}}}{(p + R_{2\rho,\text{b}})^2 + \omega_{\text{eff},\text{b}}^2} + \frac{D}{p} \quad (\text{A5})$$

where

$$D = \lim_{p \rightarrow 0} \left[p \tilde{Z}_b \right] = \frac{g(0)}{(k_b + R_{1b})(\Delta\omega_b^2 + (k_b + R_{2b})^2) + (k_b + R_{2b})\omega_{1,\text{hard}}^2} \quad (\text{A6})$$

$$c_b^{R_{1\rho, \text{fast}}} = \lim_{p \rightarrow -R_{1\rho, \text{fast}}} \left[(p + R_{1\rho, \text{fast}}) \tilde{Z}_b \right] = \frac{-g(-R_{1\rho, \text{fast}})}{\kappa}. \quad (\text{A7})$$

κ is defined in Equation 27. $c_b^{\cos, \omega^{\text{eff}}, b}$ and $c_b^{\sin, \omega^{\text{eff}}, b}$ can then be determined by initial conditions, as discussed elsewhere,¹⁷ and the final results are given in Equations 25 and 26.

A3 | Numerical calculation of component amplitudes under CW irradiation

The accuracy of the analytic solutions for component amplitudes can be checked by comparisons with the numerical solutions, which are found by rewriting Equation 14 as:

$$\frac{d\vec{M}_n}{dt} = \mathbf{A}\vec{M}_n + \vec{b},$$

where $\vec{M}_n$ is the normalized magnetization (hence the subscript 'n'). This has the solution:

$$\begin{aligned}
\vec{M}_n &= e^{At} \begin{pmatrix} \vec{M}_n^i - \vec{M}_n^{ss} \\ \end{pmatrix} + \vec{M}_n^{ss} = \mathbf{V} e^{\mathbf{D}t} \mathbf{V}^{-1} \begin{pmatrix} \vec{M}_n^i - \vec{M}_n^{ss} \\ \end{pmatrix} + \vec{M}_n^{ss} \\
&= [e^{\lambda_1 t} \vec{v}_{\lambda_1} \quad e^{\lambda_2 t} \vec{v}_{\lambda_2} \quad \dots] \begin{bmatrix} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_1 \\ \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_2 \\ \vdots \end{bmatrix} + \vec{M}_n^{ss} \\
&= \sum_{j=1}^6 e^{\lambda_j t} \vec{v}_{\lambda_j} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_j + \vec{M}_n^{ss} = e^{\lambda_1 t} \vec{v}_{\lambda_1} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_1 \\
&\quad + e^{\lambda_2 t} \vec{v}_{\lambda_2} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_2 + e^{\text{Re}[\lambda_3]t} \cos(\text{Im}[\lambda_3]t) 2 \text{Re} \left[\vec{v}_{\lambda_3} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_3 \right] \\
&\quad - e^{\text{Re}[\lambda_3]t} \sin(\text{Im}[\lambda_3]t) 2 \text{Im} \left[\vec{v}_{\lambda_3} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_3 \right] \\
&\quad + e^{\text{Re}[\lambda_5]t} \cos(\text{Im}[\lambda_5]t) 2 \text{Re} \left[\vec{v}_{\lambda_5} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_5 \right] \\
&\quad - e^{\text{Re}[\lambda_5]t} \sin(\text{Im}[\lambda_5]t) 2 \text{Im} \left[\vec{v}_{\lambda_5} \left(\mathbf{V}^{-1} (\vec{M}_n^i - \vec{M}_n^{ss}) \right)_5 \right] + \vec{M}_n^{ss} \\
&\equiv \frac{1}{c} R_{1\rho} e^{-R_{1\rho} t} + \frac{1}{c} R_{1\rho, \text{fast}} e^{-R_{1\rho, \text{fast}} t} + \frac{1}{c} \cos(\omega_{\text{eff}, a}) e^{-R_{2\rho, a} t} \cos(\omega_{\text{eff}, a} t) \\
&\quad + \frac{1}{c} \sin(\omega_{\text{eff}, a}) e^{-R_{2\rho, a} t} \sin(\omega_{\text{eff}, a} t) + \frac{1}{c} \cos(\omega_{\text{eff}, b}) e^{-R_{2\rho, b} t} \cos(\omega_{\text{eff}, b} t) \\
&\quad + \frac{1}{c} \sin(\omega_{\text{eff}, b}) e^{-R_{2\rho, b} t} \sin(\omega_{\text{eff}, b} t) + \vec{M}_n^{ss}.
\end{aligned}
\tag{A8}$$

$\vec{M}_n$ has initial value $\vec{M}_n^i$ and steady-state value $\vec{M}_n^{ss}$. $\mathbf{V}$ is a matrix whose columns are the six eigenvectors v_{λ_j} of $\mathbf{A}$ corresponding to the six eigenvalues λ_j . $\mathbf{D}$ is a diagonal matrix with elements λ_j . The derivation uses the fact that there are two sets of eigenvalues/eigenvectors conjugate pairs (as this is an underdamped system for reasonable parameter choices), which we have arbitrarily assigned to the third/fourth and fifth/sixth indices. We use conjugate relations to isolate the cosine and sine contributions.

Using MATLAB R2016b, we numerically calculate the solutions on a component-by-component basis, where $c_a^{R1\rho}$ and $c_b^{R1\rho}$ are the third and sixth components, respectively, of $\vec{c}^{R1\rho}$ and likewise for each component amplitude.

A4 | Steady-state magnetization under repeated square pulse irradiation

During the pause after n square pulse irradiations, the z -magnetization evolves according to:

$$\begin{bmatrix} Z_a(t_d + n(t_p + t_d)) \\ Z_b(t_d + n(t_p + t_d)) \end{bmatrix} = \mathbf{G}_{\text{pause}} \begin{bmatrix} Z_a(n(t_p + t_d)) \\ Z_b(n(t_p + t_d)) \end{bmatrix} + \vec{h}_{\text{pause}} \quad (\text{A9})$$

where, after taking the first order in the Taylor series in $k_b^{22,23}$:

$$\mathbf{G}_{\text{pause}} \approx \begin{bmatrix} f_b e^{-k_b t_d} + (1 - f_b) e^{-R_{1a} t_d} & -f_b e^{-k_b t_d} + f_b e^{-R_{1a} t_d} \\ -e^{-k_b t_d} + e^{-R_{1a} t_d} & e^{-k_b t_d} \end{bmatrix} \quad \vec{h}_{\text{pause}} \approx \begin{bmatrix} 1 - e^{-R_{1a} t_d} \\ 1 - e^{-R_{1a} t_d} \end{bmatrix} \quad (\text{A10})$$

After the next square pulse, the magnetization is:

$$\begin{bmatrix} Z_a((n+1)(t_p + t_d)) \\ Z_b((n+1)(t_p + t_d)) \end{bmatrix} = \mathbf{G}_{\text{pulse}} \begin{bmatrix} Z_a(t_d + n(t_p + t_d)) \\ Z_b(t_d + n(t_p + t_d)) \end{bmatrix} + \vec{h}_{\text{pulse}}, \quad (\text{A11})$$

where $\mathbf{G}_{\text{pulse}}$ is a large matrix determined by Equations 15 and 22, with:

$$\mathbf{G}_{\text{pulse}} = \begin{bmatrix} e^{-R_{1\rho} t_p} & 0 \\ \text{coefficients of } Z_a^i \text{ in Equations 22 – 26} & \text{coefficients of } Z_b^i \text{ in Equations 22 – 26} \end{bmatrix} \quad (\text{A12})$$

$$\vec{h}_{\text{pulse}} = \begin{bmatrix} Z_a^{\text{ss,cw}}(1 - e^{-R_1 \rho^t p}) \\ \text{terms without } Z_a^i \text{ or } Z_b^i \text{ in Equations 22 - 26} \end{bmatrix}. \quad (\text{A13})$$

The steady state comes from equating:

$$\begin{bmatrix} Z_a((n+1)(t_p + t_d)) \\ Z_b((n+1)(t_p + t_d)) \end{bmatrix} = \begin{bmatrix} Z_a(n(t_p + t_d)) \\ Z_b(n(t_p + t_d)) \end{bmatrix}, \quad (\text{A14})$$

which gives:

$$\begin{bmatrix} Z_a^{\text{ss,pul}} \\ Z_b^{\text{ss,pul}} \end{bmatrix} = (\mathbf{I} - \mathbf{G}_{\text{pulse}} \mathbf{G}_{\text{pause}})^{-1} \left(\mathbf{G}_{\text{pulse}} \vec{h}_{\text{pause}} + \vec{h}_{\text{pulse}} \right), \quad (\text{A15})$$

where $\mathbf{I}$ is the 2×2 identity matrix. Equation 28 comes from the Taylor series approximation of this result, as discussed above.

FIGURE 1.

(a) A chemical exchange saturation transfer (CEST) Z-spectrum is the steady-state normalized water z-magnetization (Z_a^{ss}) after radiofrequency irradiation at a frequency offset

ω_a from the water resonant frequency ω_a . (b) The radiofrequency irradiation pulse train consists of a series of shaped (typically Gaussian) pulses (blue line), which are approximated in this work by a train of square pulses (red line). The train is repeated until reaching a steady state, which may take hundreds of pulses. The transverse magnetization is spoiled between pulses

FIGURE 2.

$Z_a^{ss, pul}$ analytic (dots, Equations 1–3 and 5–12) *versus* numerical (lines) results as a function of irradiation offset (which changes ω_a and ω_b). Note the strong agreement, especially near the solute resonances at 3.5 ppm (amide) and 2.0 ppm (amine). Discrepancies occur at higher B_1 values, faster exchange rates and small ω_a values. As in all the figures, the plot rows correspond to no exchange ($k_b = 0.0001 \text{ s}^{-1}$, $\omega_b - \omega_a = 3.5 \text{ ppm}$), amide exchange ($k_b = 50 \text{ s}^{-1}$, $\omega_b - \omega_a = 3.5 \text{ ppm}$) and amine exchange ($k_b = 1000 \text{ s}^{-1}$, $\omega_b - \omega_a = 2.0 \text{ ppm}$). The plot columns correspond to differing roots of the mean square B_1 amplitudes. (In the continuous wave plots below, the columns correspond to simple differing B_1 amplitudes)

FIGURE 3.

$Z_a^{ss, pul}$ analytic (dots, Equations 1, 2 and 4–12) versus numerical (lines) results as a function of the B_1 -induced rotation angle when irradiating at the solute resonance ($\omega_b = 0$). Note the strong agreement for amides. This is the key result: that the analytic form accurately models the effect of solute rotation on the steady-state water magnetization, at least at the larger offsets and slower exchange rates of amides

FIGURE 4.

Short-time evolution of $Z_a(t)$ and $Z_b(t)$, together with the projection of Z_a^i along the a-pool effective field. Note that the time scale of $Z_b(t)$ variations is large relative to that of $Z_a(t)$ oscillations (at rate $\omega_{\text{eff},a}$) and short relative to that of $Z_a(t)$ exponential decay (at rate $R_{1\rho}$). Hence, for purposes of deriving the $Z_b(t)$ evolution, $Z_a(t)$ can be approximated by the projection of Z_a^i . This approximation fails for amines at large irradiation powers, where $Z_b(t)$ oscillates quickly and $Z_a(t)$ has non-trivial exponential decay

FIGURE 5.

Analytic (dots) *versus* numerically determined (lines) eigenvalues of the 6×6 evolution matrix in Equation 14. Note the strong agreement

FIGURE 6.

Analytic (Equations 15 and 16, dots) and numerical (lines) values of the a-pool component amplitudes as a function of the irradiation frequency offset. Note the reasonable agreement, as long as there is limited direct water (a-pool) rotation, which has been ignored in our analytic form. We have also ignored $R_{1\rho, fast}$ and $\omega_{eff, b}$ contributions to the a-pool, all of which give negligible contributions

FIGURE 7.

Analytic (Equations 17 and 23–27, dots) and numerical (lines) values of the b-pool component amplitudes as a function of the irradiation frequency. Note the reasonable agreement, as long as direct water (a-pool) rotation effects are limited by avoiding small offsets and high powers. We have ignored $\omega_{\text{eff}, a}$ contributions to the b-pool, which appear to give small contributions, except for fast amine exchange near $\omega_a = 0$

FIGURE 8.

Analytic (dots) *versus* numerical (lines) $Z_a(t)$ terms *versus* time, when irradiating at the solute resonance. Note the general agreement, which decreases for fast and small offset amine exchange and for high $B_1 = 6 \mu\text{T}$ irradiation amplitude

FIGURE 9.

Analytic (dots) *versus* numerical (lines) $Z_b(t)$ terms *versus* time, when irradiating at the solute resonance. Note the very strong agreement, except for amine exchange at the highest ($6 \mu\text{T}$) irradiation amplitude

FIGURE 10.

Analytic (dots) and numerical (lines) $Z_a(t)$ and $Z_b(t)$ values during two Gaussian pulses applied at the solute resonance. An $\alpha = 3\pi$ rotation is applied in order to clearly illustrate the ability of the analytic solution to accurately model solute rotations. However, note the deviations, especially at fast amine exchange rates